Predictors of Delayed Cerebral Ischemia in Patients with Aneurysmal Subarachnoid Hemorrhage with Asymptomatic Angiographic Vasospasm on Admission

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BACKGROUND: **Risk of delayed cerebral ischemia (DCI) in patients with aneurysmal subarachnoid hemorrhage (aSAH) with asymptomatic angiographic vasospasm on admission is unclear in the literature. The goal of this study is to identify predictors of clinical DCI in this group of patients.**

METHODS: **An exploratory subgroup analysis was conducted in the SAHIT (Subarachnoid Hemorrhage International Trialists) data repository to identify predictors of clinical DCI in patients with good-grade aSAH (World Federation of Neurological Surgeons grade I and II) with angiographic vasospasm on admission. Predictors considered include age, sex, systolic blood pressure at presentation, World Federation of Neurological Surgeon grade, Fisher grade, aneurysm size and location, treatment modality, hydrocephalus requiring external ventricular drain insertion, and severity of vasospasm. The predictors were ranked based on dominance analysis with R^2 as fit statistics and assessed in a set of logistic regression analysis models.**

RESULTS: **Four data sets out of 16 studies in the SAHIT database were analyzed, with a total of 4125 patients. One hundred and ninety-one patients (4.6%) had asymptomatic angiographic vasospasm at admission. Of those, 78 patients (40.8%) developed clinical DCI. Univariate analysis showed significant associations between severe vasospasm on admission and development of clinical DCI (odds ratio, 9.5, 95% confidence interval, 2.07–43.50; $P = 0.004$). None of the studied predictors was associated with the development of clinical DCI on multivariate analysis.**

CONCLUSIONS: **Asymptomatic angiographic vasospasm in patients with good-grade aSAH on admission is uncommon. Further studies are needed to identify high-risk patients for the development of DCI in the context of asymptomatic early vasospasm.**

INTRODUCTION

Delayed cerebral ischemia (DCI) is one of the leading causes of morbidity and mortality after aneurysmal subarachnoid hemorrhage (aSAH). Up to one third of patients with aSAH develop DCI. Death and permanent severe neurologic deficits occur in 30% of patients with aSAH as a result of DCI.[1,2] Early detection and management of DCI are critical to improve patients' outcome and survival.[1]

The prevalence of early angiographic vasospasm (within 48 hours from ictus) in aSAH is estimated to be around 9.8%.[3] Early

Key words
- Aneurysmal subarachnoid hemorrhage
- Delayed cerebral ischemia
- Vasospasm

Abbreviations and Acronyms
aSAH: Aneurysmal subarachnoid hemorrhage
CONSCIOUS-1: Clazosentan in preventing the occurrence of cerebral vasospasm following an aneurysmal subarachnoid hemorrhage
DCI: Delayed cerebral ischemia
EPO: Acute systemic erythropoietin therapy to reduce delayed ischemic deficits following aneurysmal subarachnoid hemorrhage
STATIN: Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage
TIRILAZAD: 5 studies of randomized double-blind vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage
WFNS: World Federation of Neurosurgical Societies

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Table 1. Definitions for Vasospasm and Clinical Delayed Cerebral Ischemia in the Studies Included

Variable in Each Study	Definition	Diagnostic Modality
Vasospasm		
STATIN	Mean flow velocities >1.2 m/second with LR >3 (severe vasospasm if >2.0 m/second with LR >3)	TCD
CONSCIOUS-1	Reduction in arterial diameter on DSA compared with baseline images. TCD criteria: an LR ≥3, a mean MCA or ACA flow velocity >200 cm/seconds, or an increase >50 cm/second/24 hours	DSA or TCD
EPO	According to 3 TCD criteria: 1) mean flow velocity >1.2 m/second (>2.0 m/second for severe vasospasm); 2) LR >3; and 3) an increase in mean flow velocity >0.5 m/second within 24 hours	TCD
TIRILAZAD	Reduction in arterial diameter on DSA compared with baseline images	DSA
Clinical DCI		
STATIN	Development of focal deficits or a drop in the GCS by ≥2 points. DCI was also defined as vasospasm related if it was associated with vasospasm on TCD	Clinical and TCD
CONSCIOUS-1	Vasospasm on DSA or TCD that is associated with neurologic worsening (a decline of ≥2 points in the modified GCS or an increase of ≥2 points in the abbreviated NIHSS for at least 2 hours)	Clinical and TCD or DSA
EPO	New focal neurologic deficit or reduction in the GCS ≥2 points and further categorized as vasospasm related if the criteria for vasospasm on TCD were met	Clinical and TCD
TIRILAZAD	Reduction in the GCS ≥2 points or a 2-point increase in the motor score of the NIHSS lasting for at least 8 hours	Clinical (imaging was not mandatory but recommended)

LR, Lindegaard ratio; TCD, transcranial Doppler; DSA, digital subtraction angiography; MCA, middle cerebral artery; ACA, anterior cerebral artery; DCI, Delayed cerebral ischemia; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

vasospasm on admission is an independent predictor for unfavorable outcomes in aSAH.[3,4] Furthermore, several studies of early angiographic vasospasm[3,5,6] have shown significant association between early vasospasm and DCI. However, these studies did not examine asymptomatic good-grade patients or predictors of DCI within those patients. Therefore, the aim of this study is to perform a pooled analysis of a large individual-patient database to determine if there are any predictors of DCI in this group of patients.

METHODS

Patients and Studies Selection

We performed an exploratory analysis in the SAHIT (Subarachnoid Hemorrhage International Trialists) data repository.[7] The SAHIT data repository was derived from 16 major randomized controlled trials and unselected prospective hospital cohorts. A search for all the studies with "admission vasospasm" as a variable was performed. Patients with World Federation of Neurosurgical Societies (WFNS) grade I and II were included because those are the only groups that can be clinically assessed and deemed asymptomatic if they have angiographic vasospasm within 48 hours from ictus. Patients who presented after the third day of the ictus, patients with WFNS grade greater than II, patients with no vascular imaging (computed tomography or catheter angiogram), and patients with focal neurologic deficits on admission were excluded.

The studies that were included in our analysis were:

1) Phase 1 randomized placebo-controlled trial Effects of Acute Treatment With Pravastatin on Cerebral Vasospasm, Autoregulation, and Delayed Ischemic Deficits After Aneurysmal Subarachnoid Hemorrhage (STATIN)[8]
2) Phase 2b study Clazosentan in Preventing the Occurrence of Cerebral Vasospasm Following an Aneurysmal Subarachnoid Hemorrhage (CONSCIOUS-1)[9]
3) Phase 2 randomized double-blind placebo-controlled trial Acute Systemic Erythropoietin Therapy to Reduce Delayed Ischemic Deficits Following Aneurysmal Subarachnoid Hemorrhage (EPO)[8,10]
4) Five studies of randomized double-blind vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage (TIRILAZAD)[11-15]

Outcomes

The primary outcome was the development of clinical DCI (delayed ischemic neurologic deficit). The potential predictors that were studied: age, sex, systolic blood pressure at presentation, WFNS grade (I vs. II), Fisher grade (grade I and II vs. grade III and IV), aneurysm size (≤12 mm vs. 13–24 mm vs. ≥25 mm), treatment modality (coiling vs. clipping), aneurysm location (anterior vs. posterior circulation), hydrocephalus requiring external ventricular drain insertion, and severity of vasospasm. Table 1 lists all definitions for vasospasm and DCI in the studies that were included.

Statistical Analysis

The distribution of baseline characteristics are presented by frequency numbers for categorical variables and by mean with standard deviation for continuous variables. Univariate analysis of predictors (adjusted to fixed effect of study) was conducted using